Performance of case definitions used for influenza surveillance among hospitalized patients in a rural area of India

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Objective To assess case definitions for influenza in a rural community in India.

Methods Residents of the study area who were hospitalized for any acute medical condition for at least one night between May 2009 and April 2011 were enrolled. Respiratory specimens were collected and tested for influenza viruses in a reverse-transcription polymerase chain reaction (PCR). The PCR results were taken as the "gold standard" in evaluating the performance of several case definitions.

Findings Of the 3179 patients included in the final analysis, 21% (665) were PCR-positive for influenza virus, 96% reported fever and 4% reported shortness of breath. The World Health Organization (WHO) case definition for severe acute respiratory illness had a sensitivity of 11% among patients aged < 5 years and of 3% among older patients. When shortness of breath was excluded from the definition, sensitivities increased (to 69% and 70%, respectively) and corresponding specificities of 43% and 53% were recorded. Among patients aged ≥ 5 years, WHO's definition of a case of influenza-like illness had a sensitivity of 70% and a specificity of 53%. The addition of "cough and reported or measured fever" increased sensitivity to 80% but decreased specificity to 42%.

Conclusion The inclusion of shortness of breath in WHO's case definition for severe acute respiratory illness may grossly underestimate the burden posed by influenza in hospitals. The exclusion of shortness of breath from this definition or, alternatively, the inclusion of "cough and measured or reported fever" may improve estimates of the burden.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Case definitions for influenza surveillance need to be simple, easily understood and easily implemented. The international standardization of such case definitions is difficult, partly because the optimal choice of case definition depends on the population involved and the objectives of the surveillance. The World Health Organization (WHO) arranged a consultation on this topic in 2011 and is currently developing a document to describe minimum global standards for influenza surveillance case definitions. In the surveillance of severe influenza requiring hospitalization, the WHO currently recommends a particular case definition for severe acute respiratory illness: "cough or sore throat, plus measured fever, shortness of breath and need for hospitalization" (Table 1). In the surveillance of outpatient influenza, however, WHO recommends using the case definition for influenza-like illness (measured fever plus cough or sore throat). Despite this recommendation, in some countries a case definition for acute respiratory illness is used to evaluate outpatient influenza.

The case definitions used in national and regional influenza surveillance programmes often differ from those recommended by WHO.[1–8] However, most case definitions used for influenza surveillance include measured or reported fever as well as cough and/or sore throat. Some also include constitutional symptoms, such as joint pain, myalgia, headache and/or malaise. A case definition for febrile acute respiratory illness has been used in the detection of influenza in research settings.[9]

The performance of influenza case definitions has been evaluated many times but only among ambulatory or hospitalized patients with fever or respiratory symptoms.[10–20] Such evaluations may have missed influenza cases with atypical clinical presentations, particularly those caused by acute exacerbations of underlying disease. In the Hong Kong Special Administrative Region of China and in the United States of America, > 75% of all cases of influenza-associated severe disease have been found to be classified not as influenza but under the underlying condition (e.g. cardiovascular disease, chronic lung disease or diabetes) that placed the individuals at risk.[21,22]

We conducted a study to estimate the burden of hospitalized influenza in a rural community in western India between 2009 and 2011. To maximize the detection of patients with hospitalized influenza, we screened all hospital admissions and enrolled patients with any acute medical illness of recent onset, including acute exacerbations of underlying chronic conditions. After using a reverse-transcription polymerase chain reaction (PCR) to identify patients infected with influenza virus, we retrospectively evaluated the sensitivity and specificity of various case definitions, including those that are commonly used for the detection of influenza among hospitalized patients.

Methods

Setting

The study area of Vadu lies in Pune district, 30 km to the north-east of Pune city, in western India. Vadu has a health-care infrastructure that is typical of a rural area in close proximity to a larger town or city in India. The public sector includes a rural hospital and primary health centres and the private sector

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Table 1. **Commonly used World Health Organization (WHO) case definitions for influenza surveillance**

Illness	Case definition
Influenza-like illness	Sudden-onset fever (> 38 °C) with cough or sore throat, in the absence of other diagnoses[a]
Severe acute respiratory illness	Cases aged ≥ 5 years should meet the case definition for ILI, require hospital admission and have shortness of breath and/or difficulty breathing. Younger cases should meet the IMCI programme case definition for either pneumonia or severe pneumonia. The definitions are as follows: – Pneumonia: cough or difficulty breathing plus a respiratory rate above 40 breaths per minute (if child aged 1–5 years) or 50 breaths per minute (if child aged 2–12 months). – Severe pneumonia (in children aged 2 months–5 years): requires hospital admission and has cough or difficulty breathing plus any of six general danger signs: inability to drink or breastfeed, vomiting of everything, convulsions, lethargy or unconsciousness, chest in-drawing and/or stridor in a calm child.
Acute respiratory illness[b]	Sudden onset, clinician's judgment that the illness is the result of infection, and at least one of four respiratory symptoms (cough, sore throat, shortness of breath and/or nasal discharge)
Febrile acute respiratory illness	Meets ARI definition and has fever

ARI, acute respiratory illness; IMCI, Integrated Management of Childhood Illness; ILI, influenza-like illness.
[a] Fever to be measured and not just based on history of fever or feverishness.
[b] The definition shown is that commonly used in the WHO European Region. WHO's global ARI definition is identical to the case definition for ILI.

includes several small general hospitals. Medical care is easily accessible. Most residents seek care in the private sector, which is largely unregulated. Hospital admission, treatment and pricing guidelines are often unclear, not standardized and subject to the providers' preferences. For the present study, surveillance for hospitalized influenza cases was conducted in 29 general public and private hospitals (with a mean of 15 beds per hospital) in and around the 22 villages of the Vadu Demographic Surveillance Area (DSA) in Pune district. In the study area, the monsoon and winter seasons run from June to September and November to February, respectively. Pune district has seasonal malaria and dengue activity. Although influenza activity peaks during the monsoon season, some circulation of influenza viruses occurs year-round.[23,24]

Patient screening and enrolment

Field-based investigators (trained non-clinical research staff) visited each study hospital every day between 1 May 2009 and 30 April 2011 and screened all patients who had been admitted in the previous 24 hours. Patients were excluded if they resided outside the Vadu DSA, if they had been admitted for trauma, elective surgery or obstetric or gynaecological conditions, and/or if they had not spent at least one night in a study hospital. After informed consent was obtained from the adults and the legal guardians of the children, all other patients admitted for any acute medical condition were enrolled, by the study physician, within 24 hours of admission. Those enrolled included patients admitted for onset of respiratory symptoms within the previous week or for acute onset of fever or history of fever within the previous week, and patients admitted for acute exacerbations of pre-existing chronic medical conditions (e.g. chronic lung disease, asthma, cardiovascular disease, stroke or diabetes). Detailed clinical information on each enrolled patient was abstracted from medical records at the time of admission and was also collected by the study physician at the time of interview.

Laboratory methods

A nasal and/or throat swab was collected from each enrolled patient. Within 2 or 3 days, the swabs from each patient were transported to the laboratories of the National Institute of Virology in Pune, at 2–8 °C, in a single vial of virus transport medium.[25] Ribonucleic acid (RNA) was then extracted from a subsample (50 µl) of each specimen by using a Magmax-96 viral isolation kit (Ambion®, Life Technologies Corporation, Paisley, Scotland) according to the manufacturer's instructions. Two real-time PCRs were subsequently used, first to check the RNA for evidence of influenza A and B viruses and then, if the first PCR gave a positive result for influenza A virus, to identify the subtype of influenza A virus present in the specimen.[26]

Ethics

The study protocol was approved by the Ethics Review Committee of the KEM Hospital Research Centre (Pune, India), the Ethics Review Committee of the National Institute of Virology (Pune, India) and the Institutional Review Board of the Centers for Disease Control and Prevention (Atlanta, USA). Written informed consent was obtained from the adult patients who were investigated, the legal guardians of the children who were investigated and the physicians who participated in the study.

Statistical methods

The proportional distributions of the patients who were found PCR-positive for an influenza virus, split by sociodemographic status and other characteristics, were tested for heterogeneity using Fischer's exact test. The results of the PCR were used as the "gold standard" in evaluating the performance of various standard case definitions (Table 1), individual symptoms and symptom combinations in the identification of influenza. A risk-factor analysis was conducted to estimate the predictive value of various clinical symptoms in the identification of influenza. Sensitivities, specificities and (for the period when > 10% of enrolled patients were found PCR-positive for an influenza virus) positive and negative predictive values were estimated. Case definitions that included fever were evaluated by limiting the definition of fever to measured fever at the time of presentation to hospital or by expanding the definition of fever to include both measured fever and reported history of fever.

Results

Between May 2009 and April 2011, 10 080 patients were admitted to the study hospitals. Although 9426 (94%) of these patients were screened for residential and clinical eligibility, only 3391 (36% of those screened) met the inclusion criteria and were enrolled and tested for influenza. Of those en-

rolled, 3179 were included in the final analysis; the other 212 were excluded because of inadequate specimen quality ($n = 55$) or missing clinical information ($n = 157$). Overall, 665 (21%) of the patients included in the analysis were found PCR-positive for an influenza virus: 20 (3% of the PCR-positives) for seasonal A(H1N1), 109 (16%) for seasonal A(H3N2), 340 (51%) for pandemic A(H1N1)pdm09 and 196 (30%) for influenza B virus. Nasal and throat swabs were collected from most (76%) of the tested patients 3–7 days after the onset of symptoms. The other swabs were collected < 3 (13%) or > 7 days (11%) after symptom onset.

The proportion of admissions found PCR-positive for an influenza virus was significantly higher in the first year of the study period (i.e. May 2009–April 2010) than in the second year (i.e. May 2010–April 2011): 23% versus 19% ($P = 0.007$). Among PCR-positive patients, pandemic A(H1N1) pdm09 virus predominated in both the first and second years (46% and 56%, respectively), followed by the influenza B (19% and 40%, respectively) and seasonal influenza A(H3N2) viruses (29% and 4%, respectively). Most (59%) of the PCR-positive patients were aged 5–29 years but 22% were children aged < 5 years (Table 2). The positivity rate for pandemic A(H1N1)pdm09 was not significantly different from that for the seasonal influenza viruses.

Ninety (3.1%) patients had at least one underlying chronic condition: 87 (3%) were aged ≥ 5 years and three (< 1%) were aged < 5 years. Among these 90 patients with underlying chronic conditions, PCR positivity was most common among those with asthma (26%) or chronic obstructive pulmonary disease (13%); none of the 26 patients with underlying diabetes was PCR-positive.

Respiratory specimens from patients aged ≥ 5 years were more likely to be found PCR-positive if they had been collected within 1 week of symptom onset than if they had been collected longer after symptom onset: 22% versus 17% ($P = 0.039$). However, the corresponding values for the younger patients were not significantly different ($P = 0.296$).

Clinical signs and symptoms

Of the 337 patients aged < 5 years, 44 (13%) were found to be PCR-positive for an influenza virus. The proportion of these 337 patients who had information missing for any clinical symptom (e.g. history of fever, cough and shortness of breath) or sign (temperature or respiratory rate) was < 2%. For 5% of these children, however, no attempt was made to record any of the danger signs highlighted by WHO's guidelines for the Integrated Management of Childhood Illness (IMCI; i.e. inability to drink

Table 2. **Influenza virus positivity among the patients enrolled in study, stratified by age and by clinical and other characteristics of the patients, Vadu, India, May 2009–April 2011**

Characteristic	Age < 5 years ($n = 337$)			Age ≥ 5 years ($n = 2\,842$)		
	No. positive/ no. tested	Percentage positive	P[a]	No. positive/ no. tested	Percentage positive	P[a]
Age (years)			0.000			0.000
< 1	5/86	6		NA	NA	
1–4	39/251	16		NA	NA	
5–14	NA	NA		143/404	35	
15–29	NA	NA		348/1426	24	
30–44	NA	NA		83/554	15	
45–59	NA	NA		33/279	12	
≥ 60	NA	NA		14/179	8	
Sex			0.511			0.010
Male	24/201	12		411/1755	23	
Female	20/136	15		210/1087	19	
Underlying medical condition			0.000			0.039
None	44/331	13		611/2754	22	
Asthma	0/0	0		7/27	26	
Chronic lung disease	0/0	0		1/8	13	
Cardiovascular disease	0/1	0		2/19	11	
Diabetes	0/0	0		0/26	0	
Tuberculosis	0/0	0		1/6	17	
Neurological condition	0/2	0		0/1	0	
Time from onset to specimen collection (days)			0.296			0.039
1–7	37/293	13		555/2487	22	
> 7	7/36	19		47/279	17	
Influenza type			0.214			0.766
A(H1N1)pdm09	26/337	8		314/2842	11	
Seasonal influenza A/B	18/337	5		307/2842	11	

NA, not applicable.
[a] *P*-value for trend within each category.

or breastfeed, vomiting of everything, convulsions, lethargy/unconsciousness, chest in-drawing or stridor in a calm child). Most (93%) of the 337 patients aged < 5 years reported fever and 14% had fast breathing, but only 17% were recorded as having at least one of the IMCI danger signs. Discharge diagnosis data were available for 84% of the patients aged < 5 years; the most common discharge diagnoses for this age group were fever (80%) and pneumonia (8%).

Among the patients aged < 5 years, those found PCR-positive were no more (or less) likely to have respiratory symptoms or at least one IMCI danger sign than those found PCR-negative. Those found PCR-negative were, however, more likely to suffer from vomiting (15.3% versus 7.5%; $P = 0.047$) or diarrhoea (15.8% versus 5.8%; $P = 0.011$) than their PCR-positive counterparts (Table 3).

Among the 2842 patients aged ≥ 5 years, 621 (22%) were found PCR-positive for an influenza virus. Almost all (96%) of these patients reported fever and 3% had shortness of breath. Cough, sore throat, nasal discharge and earache were more common in the PCR-positive patients of this age group than among the PCR-negative (Table 3), but headache was rarer among the PCR-positive. Discharge diagnosis data were available for 75% of the patients aged ≥ 5 years; the most common discharge diagnoses for this

Table 3. **Clinical predictors of influenza in hospitalized patients, Vadu, India, May 2009–April 2011**

Signs and symptoms, by patient age	No. of patients positive for influenza virus/no. tested (% positive)		RR	*P*
	with symptom/sign	without symptom/sign		
Patients aged < 5 years (*n* = 337)				
Symptoms				
Fever (reported)	34/299 (11.4)	5/24 (20.8)	0.55	0.227
Cough	30/221 (13.6)	9/101 (8.9)	1.52	0.269
Sore throat	20/153 (13.1)	19/170 (11.2)	1.17	0.628
Nasal discharge	24/199 (12.1)	15/124 (12.1)	1.00	0.983
Earache/discharge	0/3 (0.0)	39/320 (12.2)	–	0.695
Fast breathing	4/43 (9.3)	33/268 (12.3)	0.76	0.634
Lethargy	0/6 (0.0)	39/317 (12.3)	–	0.481
Inability/refusal to feed	3/37 (8.1)	36/285 (12.6)	0.64	0.489
Vomiting	10/133 (7.5)	29/190 (15.3)	0.49	0.047
Diarrhoea	7/120 (5.8)	32/203 (15.8)	0.37	0.011
Seizures	1/11 (9.1)	38/312 (12.2)	0.75	0.874
Signs				
Fever (> 38.0 °C)	38/265 (14.3)	5/64 (7.8)	1.84	0.192
Tachypnea[a]	0/0	43/332 (13.0)	–	1.000
At least one IMCI danger sign[b]	5/56 (8.9)	34/265 (12.8)	0.70	0.469
Patients aged ≥ 5 years (*n* = 2842)				
Symptoms				
Fever (reported)	595/2732 (21.8)	13/46 (28.3)	0.77	0.352
Chills/rigor	550/2553 (21.5)	68/274 (24.8)	0.87	0.273
Cough	497/1791 (27.8)	121/1036 (11.7)	2.38	0.000
Sore throat	361/1162 (31.1)	257/1664 (15.4)	2.01	0.000
Nasal discharge	391/1243 (31.5)	227/1584 (14.3)	2.20	0.000
Earache/discharge	7/16 (43.8)	609/2808 (21.7)	2.01	0.090
Headache	532/2514 (21.2)	86/313 (27.5)	0.77	0.027
Muscle aches	452/2061 (21.9)	166/766 (21.7)	1.01	0.900
Chest pain	16/64 (25.0)	602/2761 (21.8)	1.15	0.572
Shortness of breath	23/78 (29.5)	551/2317 (23.8)	1.24	0.314
Vomiting	111/492 (22.6)	507/2334 (21.7)	1.04	0.711
Diarrhoea	42/225 (18.7)	575/2601 (22.1)	0.84	0.289
Seizures	0/8 (0.0)	618/2819 (21.9)	–	0.174
Confusion	0/4 (0.0)	618/2822 (21.9)	–	0.416
Signs				
Fever (> 38.0 °C)	488/2208 (22.1)	123/585 (21.0)	1.05	0.627
Tachypnea[c]	574/2661 (21.6)	41/157 (26.1)	0.83	0.241
Respiratory distress[d]	8/47 (17.0)	0/0	–	1.000

IMCI, Integrated Management of Childhood Illness; RR, relative risk.

[a] Defined as respiratory rates, in breaths per minute, of > 60, > 50 and > 40 for children aged < 2 months, 2–12 months and 1–4 years, respectively.

[b] Inability to drink or breastfeed, vomiting of everything, convulsions, lethargy/unconsciousness, chest in-drawing or stridor in a calm child.

[c] Defined as a respiratory rate of ≥ 20 breaths per minute.

[d] Defined as stridor, crepitation, wheeze or reduced air entry.

age group were viral fever (76%), malaria (7%) and enteric fever (7%).

Case definition performance

In children aged < 5 years

Of all the case definitions evaluated, that for severe acute respiratory illness gave the lowest sensitivity (11%) but also the highest specificity (87%) among the patients aged < 5 years (Table 4). When shortness of breath was excluded from this case definition (leaving "influenza-like illness with measured fever in a hospitalized patient"), the sensitivity increased to 69% while the specificity decreased to 43%. A further modification – the inclusion of reported or measured fever instead of just measured fever – resulted in another increase in sensitivity (to 87%) and another decrease in specificity (to 5%).

On its own, fever (measured or reported) appeared highly sensitive (95%) but unspecific (3%) in the detection of influenza among hospitalized children aged < 5 years. In contrast, shortness of breath appeared highly specific (86%) but had low sensitivity (11%). The combination of fever (reported or measured) plus cough gave high sensitivity (77%) and moderate specificity (33%). The corresponding positive predictive values ranged from 11–17% for the standard case definitions and 14–16% for individual signs/symptoms or sign/symptom combinations.

Table 4. **Performance of standard case definitions and sign/symptom combinations in the identification of influenza among hospitalized patients, Vadu, India, May 2009–April 2011**

Definition, by patient age	Value (%) and 95% confidence interval			
	Sensitivity	Specificity	Positive predictive value[a]	Negative predictive value[a]
Age < 5 years (*n* = 337)				
Severe acute respiratory illness (measured fever only)	11 (4.2–24.7)	87 (82.2–90.3)	11 (4.5–25.9)	86 (80.6–89.6)
Severe acute respiratory illness (reported or measured fever)	11 (4.2–24.7)	86 (81.4–89.6)	11 (4.1–24.1)	86 (80.9–89.8)
Influenza-like illness (measured fever only)	69 (53.5–81.4)	43 (37.4–49.0)	17 (11.9–23.5)	90 (83.0–94.0)
Influenza-like illness (reported or measured fever)	87 (73.2–94.4)	5 (3.2–8.5)	13 (9.2–17.3)	72 (49.1–87.5)
Acute respiratory illness	77 (61.6–87.3)	26 (21.2–31.4)	14 (10.1–19.4)	88 (78.2–93.3)
Febrile acute respiratory illness (measured fever only)	63 (47.8–75.6)	44 (38.1–49.4)	16 (11.3–22.5)	88 (81.0–92.3)
Febrile acute respiratory illness (reported or measured fever)	77 (61.6–87.3)	27 (21.9–32.1)	14 (10.1–19.6)	88 (78.7–93.5)
Individual symptoms and symptom combinations				
Reported or measured fever	95 (83.1–98.5)	3 (1.4–5.5)	14 (10.1–18.3)	78 (45.2–93.6)
Measured fever (> 38 °C)	88 (75.5–94.9)	21 (16.3–25.6)	16 (12.2–21.7)	92 (81.9–96.3)
Cough	77 (61.6–87.3)	33 (27.3–38.1)	15 (10.9–21.1)	90 (81.8–94.5)
Sore throat	51 (36.2–66.1)	53 (47.3–58.8)	16 (10.2–22.7)	88 (81.7–92.0)
Shortness of breath	11 (4.2–24.7)	86 (81.1–89.4)	10 (4.0–23.5)	86 (80.9–89.8)
Cough and reported or measured fever	77 (61.6–87.3)	33 (28.1–39.1)	16 (11.3–21.7)	90 (82.0–94.6)
Sore throat and reported or measured fever	51 (36.2–66.1)	54 (47.7–59.2)	16 (10.4–23.0)	88 (81.7–92.0)
Age ≥ 5 years (*n* = 2842)				
Severe acute respiratory illness (measured fever only)	3 (1.7–4.5)	98 (97.4–98.7)	39 (25.6–54.2)	72 (70.2–74.1)
Severe acute respiratory illness (reported or measured fever)	4 (2.5–5.7)	97 (96.4–97.9)	35 (24.3–47.2)	72 (70.1–74.1)
Influenza-like illness (measured fever only)	70 (66.3–73.5)	53 (50.7–54.9)	34 (31.6–36.9)	84 (81.2–85.6)
Influenza-like illness (reported or measured fever)	97 (95.2–98.0)	3 (2.3–3.7)	26 (24.1–27.7)	76 (65.0–83.8)
Acute respiratory illness	87 (83.8–89.1)	36 (34.3–38.3)	33 (30.5–35.1)	89 (86.6–91.1)
Febrile acute respiratory illness (measured fever only)	69 (65.0–72.2)	53 (51.1–55.2)	34 (31.3–36.5)	83 (80.7–85.1)
Febrile acute respiratory illness (reported or measured fever)	86 (83.1–88.5)	37 (34.8–38.8)	33 (30.6–35.2)	89 (86.3–90.8)
Individual symptoms and symptom combinations				
Reported or measured fever	98 (96.3–98.7)	2 (1.0–2.1)	26 (24.0–27.5)	68 (52.0–79.9)
Measured fever (> 38 °C)	80 (76.5–82.8)	21 (19.5–22.9)	26 (23.9–27.9)	74 (70.3–78.1)
Cough	80 (77.1–83.3)	41 (39.3–43.4)	33 (30.7–35.5)	86 (83.9–88.4)
Sore throat	58 (54.4–62.2)	64 (61.7–65.7)	37 (33.8–39.9)	82 (79.7–83.7)
Shortness of breath	4 (2.6–5.9)	97 (96.0–97.6)	33 (23.0–44.5)	72 (70.1–74.1)
Myalgia	73 (69.5–76.4)	27 (25.3–29.0)	26 (23.7–27.8)	74 (70.1–77.0)
Headache	86 (83.1–88.5)	10 (9.0–11.6)	25 (23.6–27.4)	72 (66.4–76.4)
Cough and reported or measured fever	80 (76.1–82.5)	42 (40.2–44.3)	33 (30.7–35.6)	86 (83.7–88.2)
Sore throat and reported or measured fever	58 (54.0–61.8)	64 (62.1–66.1)	37 (33.8–39.9)	82 (79.7–83.7)
Influenza-like illness (measured fever) and either myalgia or headache	63 (59.0–66.7)	56 (53.9–58.6)	29 (26.9–32.0)	84 (82.1–85.7)
Influenza-like illness (reported or measured fever) and either myalgia or headache	77 (73.8–80.4)	45 (42.4–47.1)	22 (20.1–23.7)	78 (75.1–80.8)

[a] Calculated for the period when > 10% of the tested patients were found positive for an influenza virus (June 2009–October 2010).

The corresponding negative predictive values were all > 70%.

In patients aged ≥ 5 years

Among the patients aged ≥ 5 years, case definition for severe acute respiratory illness again had low sensitivity (3%) but high specificity (98%). When shortness of breath was excluded from this definition, sensitivity increased to 70% but specificity decreased to 53%. The case definition for acute respiratory illness gave even better sensitivity (87%) but lower specificity (36%). The addition of measured fever to this case definition lowered sensitivity, whereas the addition of reported fever had no effect on sensitivity or specificity. On their own, fever and shortness of breath performed similarly among patients aged ≥ 5 years as among the younger patients. Two constitutional symptoms, headache and myalgia, each had high sensitivity (86% and 73%, respectively) but low specificity (10% and 27%, respectively). The combination of measured fever with either cough or sore throat (i.e. influenza-like illness with measured fever) gave high sensitivity (70%) with moderate specificity (53%). Including a constitutional symptom (myalgia or headache) in the case definition of influenza-like illness decreased sensitivity (from 70% to 63%) but slightly increased specificity (from 53% to 56%). The corresponding positive predictive values for the standard case definitions (26–39%) were similar to those calculated for individual signs/symptoms and symptom combinations. As in the younger patients, all of the corresponding negative predictive values exceeded 70%.

Discussion

In the present study, the sensitivity and specificity of various case definitions for influenza were evaluated among > 3000 patients hospitalized with acute medical illness in hospitals in rural western India. Very few published studies have evaluated influenza case definitions among hospitalized patients with a similarly broad spectrum of acute illness, including non-respiratory illness.[17,27] Although WHO's case definition for severe acute respiratory illness has frequently been used to screen for influenza among hospitalized patients, our findings indicate that the use of this case definition (both among hospitalized children aged < 5 years and among older hospitalized patients) results in a low detection of influenza cases, although those meeting the case definition are likely to harbour an influenza virus. Similarly low sensitivities have been recorded for this case definition in other studies, at least among patients aged ≥ 5 years.[27] Since, in the present study, patients were checked for shortness of breath, difficulty breathing and tachypnea by trained study physicians, the low numbers of patients with these problems were unlikely to be attributable to under-detection. These problems may have been encountered relatively rarely in the present study because concerns raised by the influenza pandemic that occurred during the study period (i.e. the 2009 H1N1 pandemic) encouraged the patients investigated to seek medical care relatively early in their illness. The exclusion of shortness of breath from the case definition for severe acute respiratory illness (leaving a definition equivalent to influenza-like illness in a hospitalized patient) or the use of a simpler definition of "fever plus cough" improved sensitivity without substantial loss of specificity. Such simplified case definitions are also easier to apply in a surveillance setting because they require screening for fewer criteria. Broadening the case definition for influenza-like illness or the "fever plus cough" case definition, to include reported fever as an alternative to measured fever, further increased sensitivity while still keeping the screening criteria fairly simple.

Influenza case definitions have been evaluated among hospitalized patients before, but most relevant studies were, until recently, largely limited to adults hospitalized in developed countries, where the spectrum of underlying illness and access to care are, in general, substantially different from those seen in developing regions.[15–17,19] The present study, in a rural area of India, benefitted from the high volume of admissions to the study hospitals and the high prevalence of influenza in the study population. These features permitted the performances of various case definitions for influenza to be evaluated separately among hospitalized patients belonging to two age groups (i.e. children aged < 5 years and older individuals). As previously reported,[28] the clinical presentations of the hospitalized children aged < 5 years with and without influenza were similar, such that most case definitions for influenza in this age group had low specificities. Unfortunately, the signs and symptoms of influenza show substantial overlap with those of the infection with other respiratory viruses, such as respiratory syncytial virus, that account for a large proportion of hospitalizations among children aged < 5 years.[29] Since the performances of all the case definitions commonly used to screen for influenza appeared similar, whether the patients considered were aged < 5 years or ≥ 5 years, the development of a common case definition for use in both of these age groups appears reasonable.

Recently, two studies have evaluated case definitions for influenza in the developing countries of India and Kenya.[27,28] The sensitivities (69–70%) and specificities (43–53%) recorded for the case definition for influenza-like illness in the present study are similar to the corresponding sensitivities (73–78%) and specificities (49–65%) recently reported in northern India, in a study that used the same broad enrolment criteria.[27] However, the same case definition appeared less sensitive but more specific when investigated in Kenya, in a study confined to patients with acute respiratory illness.[28]

In the present study, 13% of the hospitalized patients aged < 5 years and 22% of those aged ≥ 5 years were found PCR-positive for influenza viruses. These relatively high prevalences may reflect the emergence of the novel pandemic A(H1N1)pdm09 influenza virus, the improved detection of patients with influenza (through the use of broad enrolment and testing criteria), and/or the effects of increased public and provider awareness of influenza, at least during the early pandemic period.[30]

The present study had several limitations. First, the findings apply only to hospitalized patients and not to outpatient or community settings. Second, despite the broad enrolment criteria, the proportion of enrolled patients with fever was high, indicating that infection is a leading cause of health-care seeking and hospitalization in our study population; this may not be the case in other settings. Third, an influenza pandemic occurred during the enrolment period. The investigated case definitions may have performed differently in the more common outbreaks of seasonal influenza, since the epidemiology (e.g. the age distribution of cases) and transmission dynamics of the seasonal and pandemic influenza viruses

may well differ. Moreover, the panic created early on in the pandemic, especially in relation to the pandemic's potential severity, could have altered the propensity of the general public to seek health care, at least during the first year of the present study. During influenza screening in several areas of China, the 2009 pandemic appears to have had a substantial impact on the apparent performance of case definitions of influenza-like illness.[20,31] The current (post-pandemic) surveillance for influenza in Vadu DSA should allow the generalizability of the present results, to purely seasonal influenza, to be evaluated. Fourthly, it is likely that seasonal variation in influenza activity may influence the performance of case definitions. The present study covered a two-year period, however, and it is likely that such seasonality affects the predictive values of the case definitions more than their sensitivities or specificities. The positive and negative predictive values reported in this article were calculated only for the period when the prevalence of influenza virus infection among the investigated patients exceeded 10% (i.e. June 2009–October 2010). Lastly, the number of elderly patients (in whom influenza may manifest atypically, such as without the presence of fever) enrolled in the present study was very small.

The best choice of a case definition may vary according to the aim of the investigation. For diagnostic purposes, physicians may desire a clinical case definition with high predictive values, to guide the management of illness. For studies on vaccine efficacy, a case definition with higher specificity may be preferred. For case finding or rapid identification of influenza outbreaks, public-health professionals may prefer a case definition with high sensitivity and accept a definition with relatively low specificity. Our findings indicate that, in Vadu at least, the use of WHO's standard case definition for severe acute respiratory illness, without adjusting for the definition's low sensitivity, would result in a substantial underestimate of the burden posed by hospitalized cases of influenza. The use of a simplified version of this definition that does not include shortness of breath or, alternatively, the use of a parsimonious combination of symptoms and signs, such as "cough plus measured or reported fever" would provide a more accurate estimate. Our findings should help guide the choice of case definition, based on study or surveillance-system priorities. ■

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ملخص

أداء تعريف الحالات المستخدم لترصد الأنفلونزا بين المرضى الذين تم إدخالهم إلى المستشفيات في منطقة ريفية بالهند

الغرض تقييم تعريف الحالات للأنفلونزا في أحد المجتمعات الريفية في الهند.

الطريقة تم تسجيل سكان منطقة الدراسة الذين تم إدخالهم إلى المستشفيات بسبب أي حالة طبية حادة لمدة ليلة واحدة على الأقل في الفترة من أيار/ مايو 2009 إلى نيسان/ أبريل 2011. وتم جمع العينات التنفسية واختبارها للبحث عن فيروسات الأنفلونزا في تفاعل البوليميراز المتسلسل ذي النسخ العكسي (PCR). وتم أخذ نتائج تفاعل البوليميراز المتسلسل بوصفه "المعيار الذهبي" في تقييم أداء تعريف حالات متعددة.

النتائج كان 21 ٪ (665) من إجمالي 3179 مريضاً تضمنهم التحليل النهائي إيجابيين لتفاعل البوليميراز المتسلسل لفيروس الأنفلونزا وأبلغ 96 ٪ عن حدوث حمى وأبلغ 4 ٪ عن حدوث ضيق تنفس. وكانت حساسية تعريف الحالة من قبل منظمة الصحة العالمية للاعتلالات التنفسية الحادة الوخيمة 11 ٪ بين المرضى الذين تزيد أعمارهم عن 5 سنوات و3 ٪ بين المرضى الأكبر سناً. وعندما تم استبعاد ضيق التنفس من التعريف، زادت الحساسيات (إلى 69 ٪ و70 ٪، على التوالي) وتم تسجيل السمات الخاصة المقابلة بنسبة 43 ٪ و53 ٪. وكانت نسبة الحساسية في تعريف الحالة من قبل منظمة الصحة العالمية فيما يتعلق بالاعتلالات الشبيهة بالأنفلونزا، بين من بلغوا 5 سنوات فأكثر من المرضى 70 ٪ ونسبة السمات الخاصة 53 ٪. وأدت إضافة "السعال والحمى المقاسة أو المبلغ عنها" إلى زيادة الحساسية لتصل إلى 80 ٪ ولكنها خفضت السمات الخاصة إلى 42 ٪.

الاستنتاج من المحتمل أن يقلل إدراج ضيق التنفس في تعريف الحالة من قبل منظمة الصحة العالمية للاعتلالات التنفسية الحادة الوخيمة من تقدير العبء الذي تفرضه الأنفلونزا في المستشفيات على نحو إجمالي. ومن المحتمل أن يحسن استبعاد ضيق التنفس من هذا التعريف أو إدراج "السعال والحمى المقاسة أو المبلغ عنها" في هذا التعريف من تقديرات العبء.

摘要

用于印度农村住院病人流感监测的病例定义的效果

目的 评估印度农村社区的流感的病例定义。

方法 将在研究区于2009年5月至2011年4月间因任何急性身体状况而住院至少一个晚上的居民纳入调查范围。收集呼吸道样本并在反转录聚合酶链反应（PCR）中检测是否有流感病毒。将PCR结果作为评估几个病例定义的效果的"黄金标准"。

结果 在被纳入最终分析中的3179例病人中，21%（665）流感病毒为PCR阳性，有96%报告发热，4%报告呼吸短促。世界卫生组织（WHO）的重症急性呼吸系统疾病的病例定义在年龄不到5岁的病人中的灵敏度为11%，在中老年人中为3%。如果定义中排除了呼吸短促，则灵敏度增加（分别为69%和70%），其记录的相应特异性为43%

和53%。在年龄不低于5 岁的病人中，世界卫生组织对流感样疾病的定义的灵敏度为70%，特异性为53%。如果增加“咳嗽和报告或测量的发热”，则灵敏度提高到80%，但特异性减少至42%。

结论 世界卫生组织对重症急性呼吸系统疾病的病例定义中纳入呼吸短促，可能会严重低估医院流感带来的负担。而从定义中排除呼吸短促，或者增加“咳嗽和测量或报告的发热”则可能会改进负担的估计。

Résumé

Résultats des définitions de cas utilisées pour la surveillance de la grippe chez des patients hospitalisés dans une région rurale de l'Inde

Objectif Évaluer les définitions de cas de grippe dans une collectivité rurale en Inde.

Méthodes On a inclus les habitants de la zone de l'étude, qui ont été hospitalisés pour toute affection médicale aiguë pendant au moins une nuit entre mai 2009 et avril 2011. Des échantillons respiratoires ont été collectés et testés pour les virus grippaux par une transcription inverse - réaction en chaîne par polymérase (PCR). Les résultats de la PCR ont été pris comme étalon pour l'évaluation des résultats des définitions de cas.

Résultats Sur les 3179 patients inclus dans l'analyse finale, 21% (665) étaient PCR-positifs au virus de la grippe, 96% déclaraient de la fièvre et 4% un essoufflement. La définition de cas par l'Organisation mondiale de la Santé (OMS) du syndrome respiratoire aigu sévère présentait une sensibilité de 11% chez les patients âgés de moins de 5 ans et de 3% chez les patients plus âgés. Lorsque l'essoufflement était exclu de la définition, la sensibilité augmentait (69% et 70%, respectivement) et des spécificités correspondantes de 43% et 53% étaient enregistrées. Chez les patients âgés de 5 ans et plus, la définition de cas par l'OMS du syndrome grippal présentait une sensibilité de 70% et une spécificité de 53%. L'ajout de la «toux et d'une fièvre déclarée ou mesurée» augmentait la sensibilité à 80%, mais diminuait la spécificité à 42%.

Conclusion La prise en compte de l'essoufflement dans la définition de cas par l'OMS du syndrome respiratoire aigu sévère peut sous-estimer lourdement la charge que représente la grippe dans les hôpitaux. L'exclusion de l'essoufflement de cette définition ou, de manière alternative, l'inclusion de la «toux et d'une fièvre mesurée ou déclarée» peut améliorer les estimations de la charge.

Резюме

Определения случаев, используемых для эпиднадзора за гриппом среди госпитализированных пациентов в сельской местности Индии

Цель Оценить определения случаев заболевания гриппом в сельской местности в Индии.

Методы В исследование были включены жители исследуемой местности, которые были госпитализированы с любым острым заболеванием, по крайней мере, на одну ночь в период с мая 2009 г. по апрель 2011 г. Были собраны и проанализированы дыхательные пробы на наличие вирусов гриппа в полимеразной цепной реакции с обратной транскриптазой (ПЦР). Результаты ПЦР были приняты за “золотой стандарт” в оценке осуществления определения нескольких случаев.

Результаты Из 3179 пациентов, включенных в итоговый анализ, у 21% (665) имелась положительная ПЦР на вирус гриппа, у 96% выявлено лихорадочное состояние и у 4% отмечена одышка. Чувствительность определения случая тяжелой формы острого респираторного заболевания по методике Всемирной организации здравоохранения (ВОЗ) равнялась 11% среди пациентов, не достигших пятилетнего возраста, и 3% среди пациентов в более старшем возрасте. При исключении одышки из определения повысилась чувствительность (до 69% и 70% соответственно), и была отмечена специфичность 43% и 53%. Среди пациентов в возрасте ≥ 5 лет, чувствительность определения случая гриппоподобного заболевания по методике ВОЗ равнялась 70%, и специфичность составила 53%. Добавление «кашля и подтвержденного или заявленного лихорадочного состояния» повысило чувствительность до 80%, но снизило специфичность до 42%.

Вывод Включение одышки в определение случая тяжелой формы острого респираторного заболевания по методике ВОЗ может привести к большой недооценке бремени, создаваемого гриппом в госпиталях. Исключение одышки из этого определения или, наоборот, включение «кашля и подтвержденного или заявленного лихорадочного состояния» может улучшить оценочные показатели бремени.

Resumen

Consideración de las definiciones de casos empleadas para la vigilancia de la gripe entre los pacientes hospitalizados en un área rural de India

Objetivo Evaluar las definiciones de los casos de gripe en una comunidad rural en India.

Métodos Se inscribió a los residentes del área de estudio hospitalizados durante al menos una noche por cualquier dolencia aguda entre mayo del 2009 y abril del 2011. Se recogieron muestras respiratorias a las que se efectuó una prueba por medio de una reacción en cadena de la polimerasa (RCP) para determinar la presencia del virus de la gripe. Los resultados de la RCP se tomaron como «prueba de oro» para evaluar la realización de varias definiciones de casos.

Resultados De los 3179 pacientes incluidos en el análisis final, el 21% (665) dio positivo en la RCP para el virus de la gripe, el 96% declaró tener fiebre y el 4%, dificultad para respirar. La definición de caso de la Organización Mundial de la Salud (OMS) para las afecciones respiratorias agudas graves tuvo una sensibilidad del 11% entre los pacientes menores de cinco años y del 3% entre pacientes de más edad. La sensibilidad aumentó (al 69% y al 70%, respectivamente) y se registraron particularidades correspondientes del 43% y 53% cuando se excluyó la dificultad respiratoria de la definición. Entre los pacientes con edades inferiores a 5 años, la definición de la OMS de los casos de síndrome gripal presentó una sensibilidad del 70% y una particularidad del 53%. La sensibilidad aumentó hasta el 80% cuando se añadió «tos y fiebre declarada o medida», sin embargo, la particularidad descendió hasta el 42%.

Conclusión Incluir la dificultad para respirar en la definición de caso de la OMS para la afección respiratoria aguda grave podría subestimar en extremo la carga que la gripe representa en los hospitales. Excluir la dificultad para respirar de dicha definición o, de manera alternativa, incluir la «tos y fiebre declarada o medida» podría mejorar el cálculo de la carga.

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